

Fetal intracranial hemorrhage (fetal stroke): does grade matter?

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ABSTRACT

Objective To determine if the severity of antenatally diagnosed hemorrhagic fetal brain insults and fetal stroke detected by ultrasound and magnetic resonance imaging (MRI) predicts postnatal neurodevelopmental prognosis.

Methods The in-utero presentation and postnatal neurodevelopmental outcome of sonographically detected subdural hematoma or fetal stroke presenting as intraventricular hemorrhage (IVH) or intraparenchymal brain hemorrhage were investigated.

Results Of 33 fetuses diagnosed with hemorrhagic brain lesions, 17 were electively terminated and two suffered intrauterine fetal demise. Thirteen were liveborn, seven by Cesarean delivery and six by spontaneous vaginal delivery. One case was lost to follow-up. Eight neonates had moderate to severe neurological deficit by a mean age of 35 (range, 6–96) months. One died at 2 months of age. These nine were diagnosed with Grade III–IV IVH in utero. Four neonates had normal neurological outcome by a mean age of 41 (range, 30–48) months; these four were diagnosed with subdural hematoma ($n = 1$) or Grade I–II IVH ($n = 3$) in utero. Fourteen cases were followed up with MRI, which confirmed ultrasound findings in 10 (71%) cases. In three (21%) cases MRI diagnosis was more accurate and the severity of grading was greater than that obtained on ultrasound imaging. Unilateral left hemispheric lesions were much more common than right-sided lesions (13 vs. 1, respectively).

Conclusions An antenatal sonographic diagnosis of fetal stroke with IVH Grade III–IV or with brain parenchymal involvement appears to be associated with poor neurological outcome. MRI may contribute to the

accuracy of diagnosis, particularly in Grade II and III lesions. Left-sided unilateral lesions are more common than right-sided ones. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Fetal hemorrhagic and hypoxic-ischemic insults are pathophysiological processes that lead to antenatal brain damage and fetal stroke. These events are associated with postnatal seizure disorders, mental retardation, psychomotor delays and cerebral palsy^{1–7}. Fetal intracranial hemorrhages (ICHs) and strokes are amenable to antenatal diagnosis by ultrasound and magnetic resonance imaging (MRI)^{8–10}.

The classification of ICH includes five major types: intraventricular hemorrhage (IVH), cerebellar, subdural, primary subarachnoid hemorrhages and miscellaneous intraparenchymal hemorrhages. IVHs are the most common variety of neonatal ICH and are characteristic of the immature brain. IVHs are subdivided according to their severity into four grades; the first three grades are limited to the ventricles, while the fourth grade includes parenchymal involvement occurring in the most severe cases³.

Hypoxic-ischemic events in premature neonates occur mainly in the brain parenchyma in the hippocampus, pons and cerebellum causing selective neuronal necrosis, and in the periventricular germinal matter causing periventricular leukomalacia, while in term neonates cortical injury is more common³. The neurodevelopmental outcome of bleeding into the ventricles ranges from hemorrhage absorption and resolution without residual deficit, to brain damage that leads to neurological and mental deficits, epilepsy and in extreme cases to fetal or neonatal death³.

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Fetal brain ischemic events, although diagnosed rarely, are usually followed by neurological deficiencies later in life^{2,3,7-10}. However, the true incidence of ischemic events is not known and theoretically it is possible that small ischemic events may be missed and remain undiagnosed³⁻⁵.

Different scoring systems have been developed to predict the prognostic significance of fetal IVH. These scores depend upon ventricular enlargement and the presence or absence of brain parenchymal damage¹¹⁻¹⁴.

Ultrasonography, and more recently MRI, allows non-invasive assessment of antenatal fetal brain hemorrhagic and ischemic lesions. We sought to correlate the extent of fetal brain imaging findings to neonatal and pediatric neurobehavioral development. Ghi *et al.*¹⁴ found that the extent and severity of fetal brain lesions might predict postnatal neurological outcome. We studied this hypothesis in a cohort of affected fetuses treated in our institution in the last 8 years since the implementation of regular use of both ultrasound and MRI examination of these fetuses.

METHODS

Thirty-three cases of fetal ICH were detected between June 1996 and May 2004 in patients undergoing routine or targeted prenatal sonographic examinations in the university hospitals of Hadassah Ein Kerem and Hadassah Mount Scopus, both tertiary obstetric centers in Jerusalem, Israel. In most cases ultrasound was performed transabdominally, the transvaginal approach being used when appropriate, with HDI 5000 (ATL, Bothell, WA, USA) with 3.5- and 5-MHz transabdominal probes and a 5.0-MHz transvaginal probe. In each case a series of initial and follow-up obstetric sonograms were performed (range, 2-7 sonograms). Serial examinations are detailed for those cases in which ultrasound progression of the lesion(s) was noted (Table 1). At each sonographic examination a detailed targeted organ scan of fetal anatomy was performed. All examinations were performed and analyzed by one of two expert sonographers with advanced training in prenatal ultrasonographic diagnosis (S.Y. and M.N.).

Axial, coronal and sagittal planes were used to characterize ICH by means of the following parameters: location, size and echogenic appearance of the hemorrhage, absence or presence of ventriculomegaly, the presence of hyper-echogenic and sometimes indented ventricular walls, and intraventricular or parenchymal hyperechogenic foci suggestive of clots. IVH was diagnosed by the demonstration of sonographic findings suggestive of blood clots within the ventricles. Color Doppler velocimetry of fetal umbilical and middle cerebral arteries was used to evaluate the associated hemodynamic changes.

MRI studies (MRI, Sigma Horizon LX, GE Medical Systems, Milwaukee, WI, USA) were performed in 14 cases following sonographic diagnosis. After a localizing gradient-echo sequence, ultra-fast T2-weighted single-shot fast spin-echo (HASTE) MRI images were obtained

according to fetal position in the axial, coronal and sagittal planes with the following parameters: 1521/90/1 (TR/TE/NEX), bandwidth of 31.5 kHz, field of view of 32 × 40 cm, matrix (320 × 224), slice thickness/gap of 4/1 mm.

The evolution of the ultrasonographic pattern of IVH is that fresh blood clots appear as homogeneously echogenic areas, separate from the choroid plexus. Over the course of several weeks some blood clots develop a complex appearance, with an external echogenic lining and an internal sonolucent core¹⁴.

IVH was categorized following the classification commonly used in neonates with some modifications⁷. Grade I was defined as hemorrhage limited to the subependymal matrix. Grade II was defined as a clear hemorrhage spillover to the ventricles filling less than 50% of the lateral ventricle and without ventriculomegaly of greater than 15 mm in the transverse diameter of the lateral ventricular atrium. Grade III was diagnosed when spillover to ventricles with flooding of 50% or more of one or both lateral ventricles accrued accompanying ventriculomegaly, but with no apparent brain parenchymal injury. In this category we, as others¹⁴, decided to include IVHs associated with a diameter exceeding 15 mm in the transverse diameter of the lateral ventricular atrium. Grade IV included Grade I-III hemorrhages accompanied by hemorrhage in a large part of the periventricular parenchyma. These cases were commonly associated with sonographic demonstration of diffuse intracerebral echogenicity obscuring one or both lateral ventricles with an involvement of cerebral parenchyma, and on MRI usually appeared as a hypointense area on T2-weighted images and frequently as a hyperintense area on T1-weighted images. In the present study we included intracerebral and intracerebellar hemorrhages as well as porencephaly within this grade (Figures 1 and 2).

Detailed evaluation for possible etiology of intracranial hemorrhagic or ischemic events was performed in all cases including maternal history of drug exposure, TORCH screen and tests for alloimmune thrombocytopenia. Fetal karyotype and cytomegalovirus assay using polymerase chain reaction were performed when relevant. Patients received counseling by a team that included a perinatologist, a geneticist and pediatric neurologist and, in most cases, a pediatric neurosurgeon. All live-born infants underwent postnatal evaluation and brain imaging. Prenatal and neonatal sonograms, computed tomography or MRI, medical records and clinical course were retrospectively reviewed. We also evaluated the medical records of all the cases for perinatal mortality and adverse neurological sequelae, defined as cerebral palsy, seizure disorders, mental retardation, moderate and severe mental developmental disturbances and retarded psychomotor development, based on their periodic follow-up visits, carried out at child neurology clinics. Pathological examination of both fetus and placenta was obtained after fetal or neonatal death upon obtaining parental consent. However, for religious reasons many couples

Table 1 Summary of prenatal diagnosis, clinical pregnancy outcome, and follow-up of Grade I–IV cases of fetal intracranial hemorrhage

Case	MA	GA	Ultrasound (Grade)	MRI	Associated findings	Clinical outcome	Postnatal diagnosis
1	27	24	Subdural hematoma, reversed flow in middle cerebral artery		None	TOP 25 weeks	PM confirmed ultrasound findings
2	22	21	Subdural supratentorial posterior hematoma	Confirmed ultrasound findings	None	SD 39 weeks	No apparent neurological impairment at 40 months
3	37	36	Spontaneous regression		None	TOP 25 weeks	PM: normal brain; normal karyotype
	22	22	Bilateral VM, 12 mm, with subependymal hemorrhage (Grade I)				
4	22	26	Unilateral left subependymal hemorrhage (Grade I)		Oligohydramnios, single UA	No follow-up	No follow-up
5	34	22	Left VM 11 mm; IVH (Grade II)	Bilateral VM 14 mm, IVH of greater diameter (Grade II)	None	TOP 26 weeks	PM confirmed findings
6	29	28	Monochorionic diamniotic twins. Twin B: IUFD at 22 weeks. Twin A: left subependymal hemorrhage and bilateral asymmetric VM (Grade II)	Twin A: left subependymal hemorrhage and more extensive asymmetric VM (Grade III)	IUGR, polyhydramnios, hyperchogenic bowel, mild ascites	TOP, Twin A 31 weeks	PM. Twin B: macerated fetus. Twin A: IVH and ICEH (Grade IV)
7	24	18	Bilateral VM, 11 mm; enlarged 3rd ventricle; left lobe tumor; bilateral IVH (Grade II)		None	TOP 20 weeks	PM confirmed findings, with brain tumor (Grade II)
8	31	22	Left VM 13 mm; cerebral and cerebellar calcifications; diffuse IVH (Grade II)		Hyperchogenic bowel, ascites, reversed diastolic flow in UA	IUFD 25 weeks	PM confirmed findings
9	35	23	Bilateral VM 14 mm; dilated 3rd ventricle, bilateral IVH (Grade II)	Confirmed ultrasound (Grade II)	None	SD 38 weeks	Postpartum ultrasound confirmed IVH; spontaneous regression; normal development; follow-up at 48 months (Grade III)
10	26	28	Monoamniotic monochorionic twins. Twin A: bilateral VM 12 mm, IVH (Grade II)	Confirmed ultrasound (Grade II)	Twin A IUGR. Cord entanglement	CS 30 weeks	IVH spontaneous regression. Normal neurological development. Follow-up at 30 months (Grade III)
11	38	24	Left VM, IVH (Grade II)		Rhesus alloimmunization, persistent ascites after fetal blood transfusion	CS 34 weeks	Ultrasound confirmation of left VM. No neurological sequelae at 48 months (Grade II)
12	23	31	Left VM 16 mm, IVH (Grade III)		Hydrops fetalis	TOP 38 weeks	PM denied
13	27	30	Bilateral VM 30 mm (Grade III)		None	TOP 31 weeks	PM denied; normal karyotype
14	26	40	Bilateral VM 24 mm, IVH (Grade III)	Left VM, IVH (Grade III)	None	TOP 40 weeks	PM denied; PM CT confirmed ultrasound findings (Grade III)

(continued overleaf)

Table 1 (Continued)

Case	MA	GA	Ultrasound (Grade)	MRI	Associated findings	Clinical outcome	Postnatal diagnosis
15	25	30	Left VM 14 mm. IVH and subependymal hemorrhage (Grade III)	Revealed both IVH and ICEH (Grade IV)	None	TOP 32 weeks	Postnatal CT revealed both ICEH and IVH (Grade IV)
16	28	34	Asymmetric bilateral VM and IVH. Left 32 mm, right 17 mm	Confirmed ultrasound (Grade III)	None	CS 37 weeks	MRI revealed hemorrhagic aqueductal stenosis; VP shunt at 2 weeks, moderate motor delay; follow-up at 6 months (Grade III)
17	32	36	Left 41 mm, right 28 mm (Grade III)	Confirmed ultrasound (Grade IV)	Polyhydramnios, hyperéchogenic bowel, mild ascites, hepatomegaly	TOP 31 weeks	PM denied
	26		Left intracerebral periventricular hemorrhage (Grade IV)		None		
18	23	29	Left VM 12 mm, ICEH (Grade IV)			TOP 29 weeks	PM confirmed ultrasound findings (Grade IV)
19	23	24	Huge bilateral porencephaly, ICEH (Grade IV)		Bilateral cataract	TOP 25 weeks	PM denied; PM CT confirmed ultrasound findings (Grade IV)
20	32	34	Microcephaly, bilateral VM 13 mm, ICEH (Grade IV)		IUGR, polyhydramnios, normal karyotype	TOP 35 weeks	PM revealed extensive dystrophic calcification of brain (CMV-negative) (Grade IV)
21	25	24	Mild left VM periventricular calcifications, left temporal porencephaly (Grade IV)		Hyperéchogenic bowel	TOP 29 weeks	PM and CT confirmed ultrasound findings, (CMV-negative), normal karyotype (Grade IV)
22	41	21	Asymmetric bilateral VM. Left 16 mm, right 12 mm, ICEH, porencephaly (Grade IV)		None	TOP 22 weeks	PM and CT confirmed ultrasound findings; normal karyotype (Grade IV)
23	24	19	Bilateral VM and ICEH. Periventricular calcifications (Grade IV)		Bilateral polycystic kidney, placentomegaly	TOP 22 weeks	Carnitine palmitoyl transferase II deficiency (Grade IV)
24	28	22	Asymmetric bilateral VM and ICEH		None	TOP 25 weeks	PM confirmed ultrasound findings (Grade IV)
25	29	23	Left 25 mm Right 21 mm (Grade IV) Left VM 12mm. ICEH and cerebellar hemorrhage (Grade IV)	Confirmed ultrasound (Grade IV)	Severe IUGR, hyperéchogenic bowel (Grade IV)	IUFD 24 weeks	PM denied
26	31	32	ICEH occipital lobe (Grade IV)	Confirmed ultrasound (Grade IV)	Symmetrical IUGR	CS for fetal distress 38 weeks	Ultrasound confirmed imaging findings, mild-moderate psychomotor retardation. Follow-up at 12 months (Grade IV)

27	39	31	Asymmetric bilateral VM. Left 15 mm, right 11 mm	None	SD 40 weeks	CT confirmed porencephaly, hydrocephaly, VP shunt, shunt between lateral ventricle and porencephalic cyst, mental retardation; follow-up at 94 months (Grade IV)
	35		Left 24 mm, right 11 mm			
	40		Left porencephaly 60 × 40 mm (Grade IV)			
28	22	29	Asymmetric bilateral VM. Left 30 mm, right 18 mm	Left pyelectasis, polyhydramnios	SD 39 weeks	CT confirmed ultrasound findings. Right hemiplegia, hydrocephalus: VP shunt, blindness, mental retardation; follow-up at 96 months (Grade IV)
	38		Huge parietotemporal porencephaly (Grade IV)			
29	33	34	Left porencephalic cysts (× 2) (Grade IV)	Polyhydramnios, single UA, arthrogryposis	CS 36 weeks	CT confirmed ultrasound findings. Gastrostomy, tracheostomy. Severe neurodevelopmental retardation. Follow-up at 9 months (Grade IV)
30	36	30	Left cerebellar hemorrhage (Grade IV)	None	SD 39 weeks	Postnatal MRI revealed complete absence of left cerebellar lobe; severe neurological impairment. Follow-up at 48 months (Grade IV)
31	19	14	Missed twin	Bowel obstruction. In the surviving twin intra-abdominal calcifications, splenic infarct	SD 36 weeks, liveborn	CT confirmed ultrasound findings. Hypotony, germinal atresia, abnormal EEG, PPND at 2 months (Grade IV)
	22		Asymmetric bilateral VM. Left porencephaly, right VM 11 mm (Grade IV)			
32	27	32	Ischemic brain damage ICEH, left cerebrium 4 mm	None	CS 37 weeks, liveborn	CT confirmed imaging findings. Severe neurological impairment. Follow-up at 12 months (Grade IV)
33	32	23	IVH and left VM 15 mm, porencephaly (Grade IV)	None	CS 38 weeks	Left hemiparesis. Follow-up at 6 months (Grade IV)
			Monochorionic diamniotic twin pregnancy. Twin A: right VM and ICEH (Grade IV)			

CMV, cytomegalovirus; CS, Cesarean section; CT, computed tomography; EEG, electroencephalogram; GA, gestational age in weeks; ICEH, intracerebral hemorrhage; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; MA, maternal age in years; MRI, magnetic resonance imaging; PM, postmortem examination; PPND, postpartum neonatal death; SD, spontaneous delivery; TOP, termination of pregnancy; UA, umbilical artery; VM, ventriculomegaly; VP, ventriculoperitoneal.

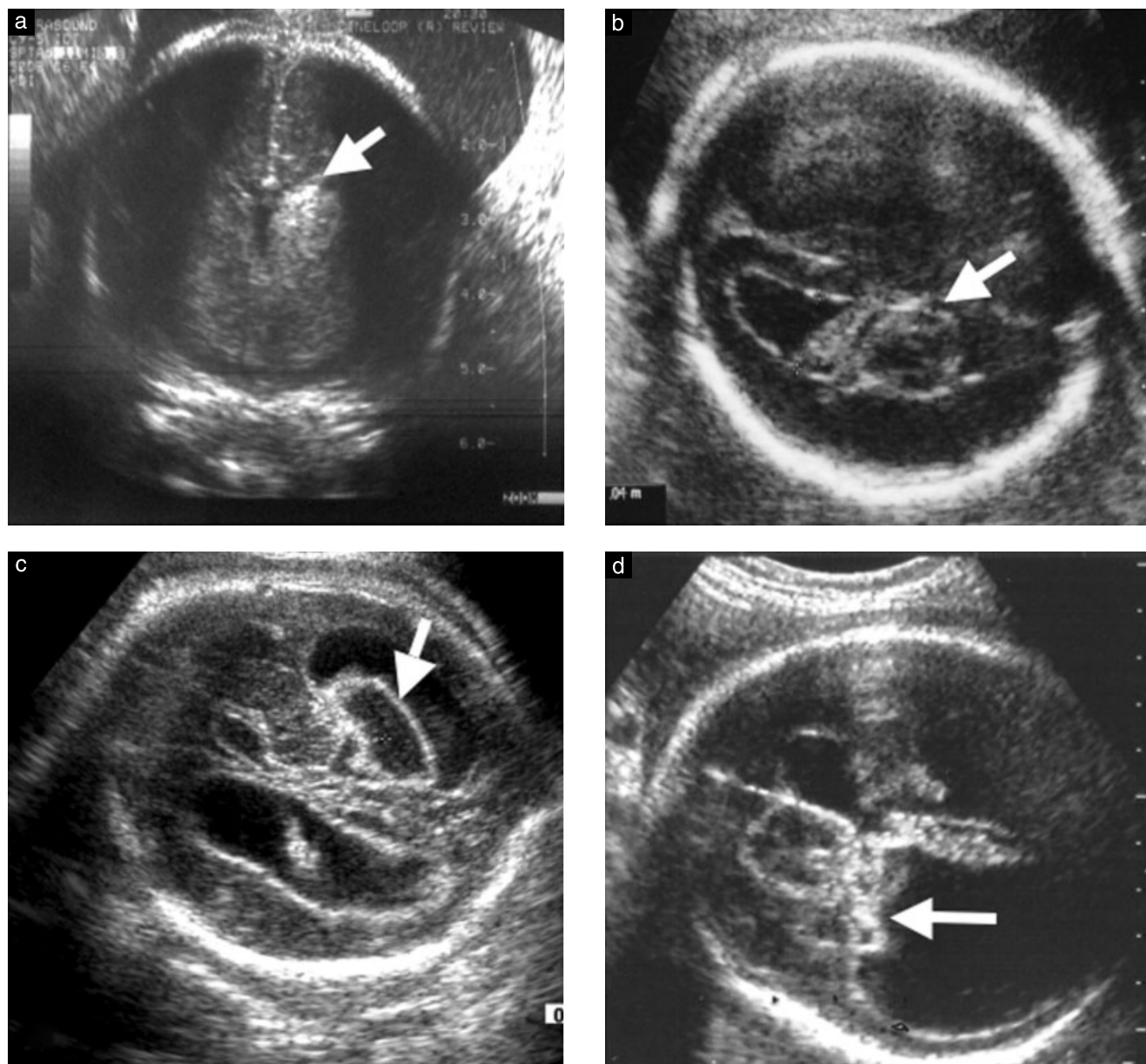


Figure 1 Sonographic demonstration of the different grades of intraventricular hemorrhage. (a) Coronal view of the brain of a mid-trimester fetus (Case 4, 26 weeks) with recent Grade I subependymal hemorrhage (arrow). (b) Axial view of mid-trimester (Case 11, 24 weeks) Grade II hemorrhage (arrow). (c) Axial view of Grade III hemorrhage with bilateral intraventricular enlargement (Case 12, 33 weeks) and organized blood clot in the ventricle (arrow). (d) Axial view of Grade IV hemorrhage with bilateral intraventricular enlargement and left porencephaly; the arrow points to intraparenchymal hemorrhage (Case 31, 22 weeks).

refused a postmortem. Statistical analysis was performed using Fisher's exact test¹⁵. The Hadassah University Hospital ethical review board approved this study for human subjects at both institutions.

RESULTS

Antenatal intracranial hemorrhagic and ischemic insults were detected in 33 cases out of 71 023 deliveries (0.46/1000 deliveries) at the authors' institutions between June 1996 and May 2004. The incidence is probably biased by the fact that the authors' institutions are tertiary referral centers and the true incidence of ICH may be much lower. Gestational ages at diagnosis ranged from

18 to 40 weeks, 20 (61%) fetuses diagnosed between 18 and 28 gestational weeks and 13 (39%) fetuses diagnosed at or after 29 gestational weeks. Two cases were sonographically diagnosed with subdural hematoma, and two with Grade I and seven with Grade II IVH. Five cases were diagnosed antenatally with Grade III IVH, and 16 with Grade IV; one fetus was found to have an ischemic lesion. The details of two cases in the present series have been previously reported^{9,16}. Ischemic fetal brain damage was diagnosed in one fetus (Case 32) after an emergency mitral valve replacement performed in a pregnant woman with stuck prosthetic mitral valve at 30 weeks of gestation. Several ultrasound examinations prior to surgery showed normal fetal anatomy and

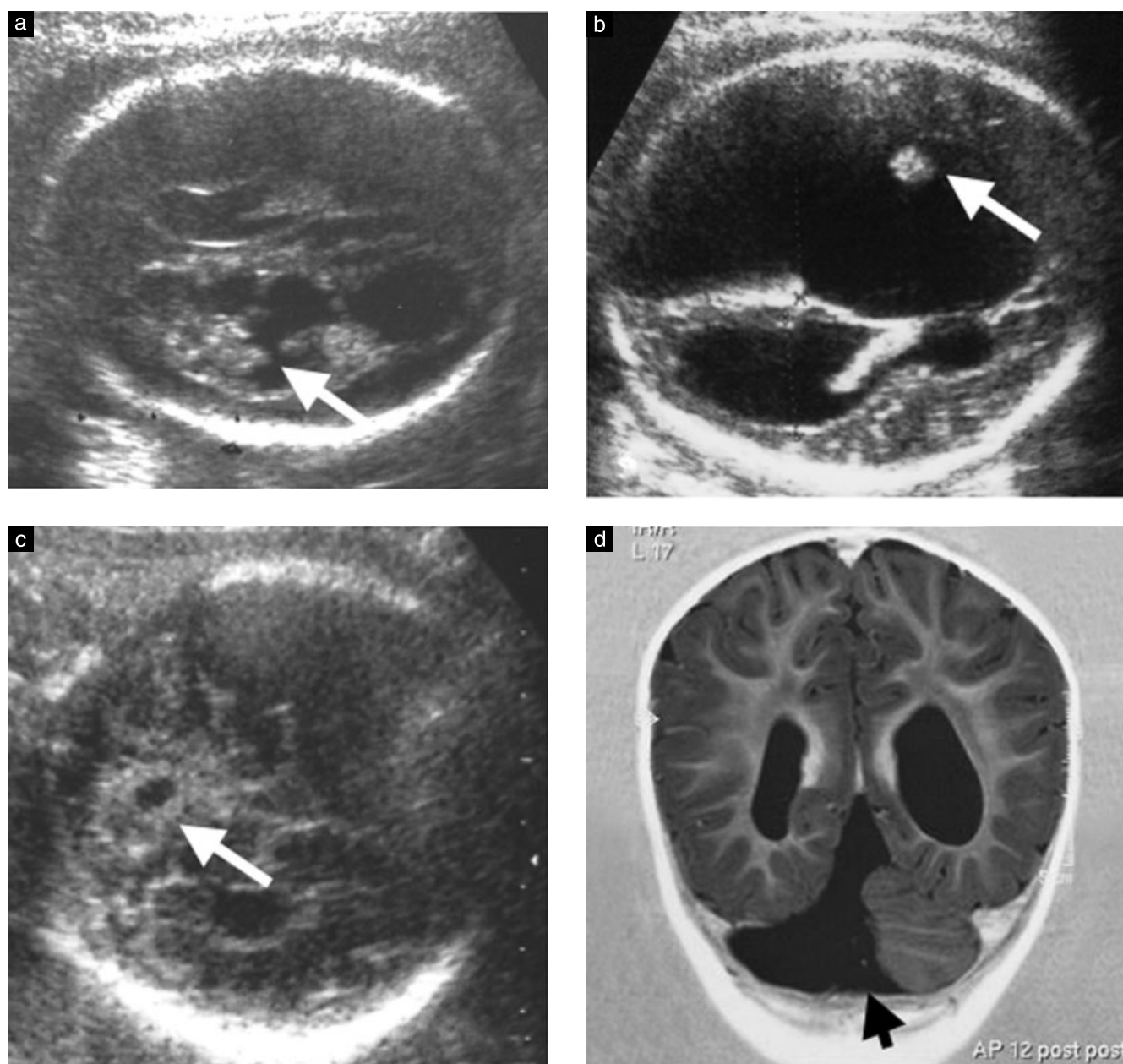


Figure 2 Grade IV fetal brain hemorrhages. (a) Ultrasound image demonstrates bilateral asymmetric ventriculomegaly; the left ventricle (arrow) is much larger than the right ventricle (Case 28, 29 weeks). (b) Ultrasound image of huge parietotemporal porencephaly with residual IVH (arrow) of the same case at 38 weeks. (c) Ultrasound image of left cerebellar hemorrhage (arrow) (Case 30, 30 weeks). (d) Postnatal magnetic resonance imaging scan of Case 30 showing absence of left cerebellar lobe (arrow).

development. During the valve replacement procedure, fetal heart rate monitoring showed a sinusoidal pattern under extracorporeal maternal oxygenation. A week later intracerebral ischemic-hemorrhagic lesion was noted followed by the evolution of bilateral porencephaly at 36 weeks (Figure 3).

Table 1 summarizes the ultrasound findings, MRI when performed, and outcome, in addition to the postmortem findings, when a postmortem examination was performed.

IVH was bilateral in 16 cases, unilateral left-sided in 13 cases, and right-sided in one case. Of the 16 bilateral IVHs, five were found to be asymmetric with left-side ventriculomegaly >25% wider than the right side. Doppler studies of umbilical artery pulsatility index

and mid-cerebral artery peak systolic velocity were normal and appropriate for gestational age in all cases.

Termination of second- and third-trimester pregnancies is permitted by law in Israel, pending the approval of a special ethics committee accredited by the Ministry of Health. In the present series, 5/11 (45%) couples with fetuses diagnosed with subdural hematoma or Grade I–II IVH and 12/22 (55%) couples with fetuses diagnosed with ischemic or Grade III–IV IVH elected to terminate their pregnancy after approval of the ethics committee at 22–40 weeks. Of the other 16 fetuses, one case was lost to follow-up (Case 4), two of the fetuses died *in utero* (Cases 8 and 25) and 13 cases were delivered at 29–40 (mean $\pm$ SD, 37.1 ± 2.7) gestational

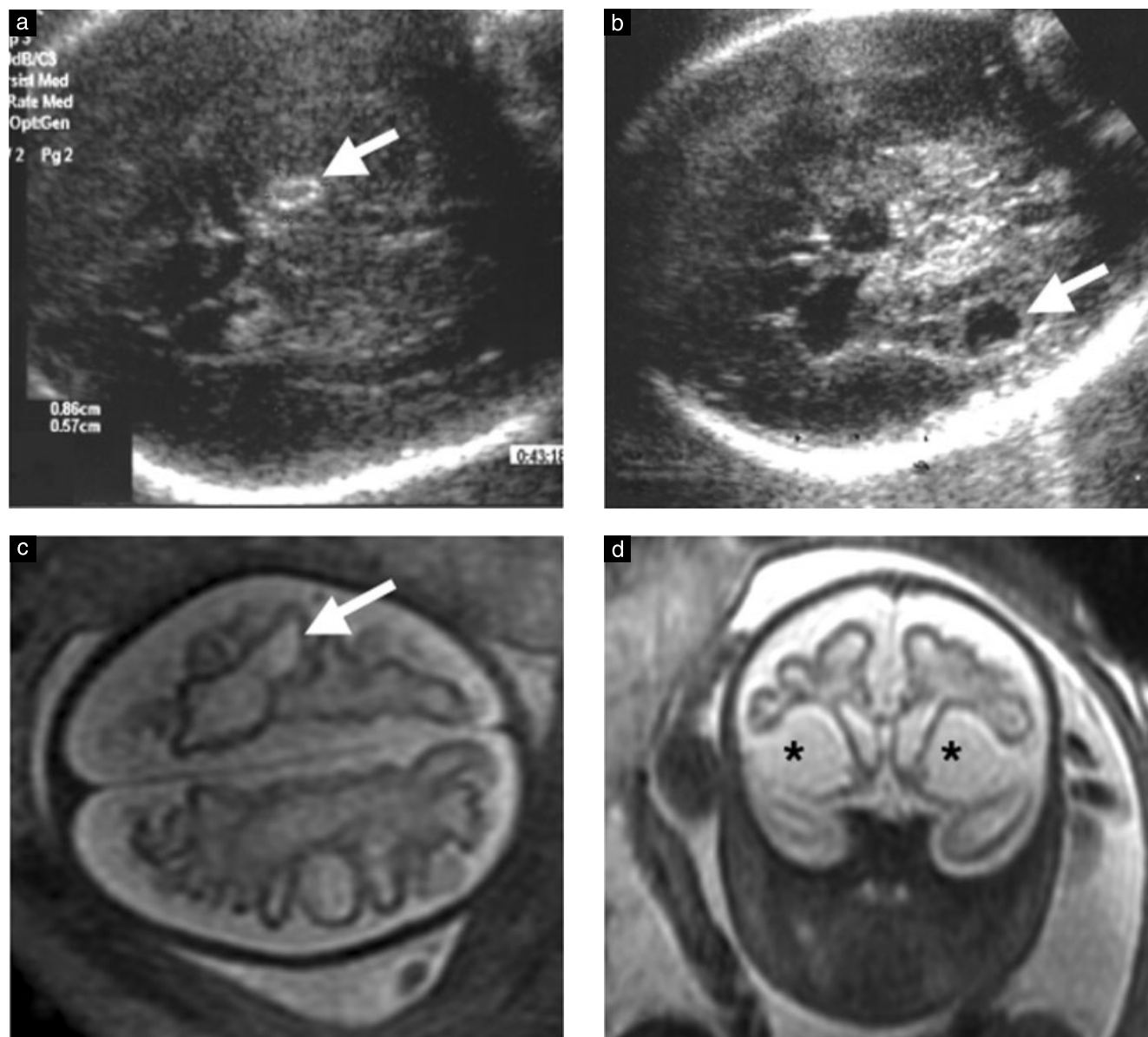


Figure 3 Fetal brain ischemia followed low maternal blood pressure during emergency mitral valve replacement (Case 32). (a) Ultrasound image of left intracerebral hemorrhage (arrow) diagnosed a week after the operation (32 weeks). (b) Ultrasound image demonstrating brain tissue liquefaction (arrow) noticed 4 weeks after the operation. (c) Magnetic resonance imaging (MRI) performed at 35 weeks with bilateral porencephaly formation; the arrow indicates intracerebral bleeding. (d) MRI coronal view of bilateral intracerebral hemorrhage (asterisks).

weeks, six (46%) vaginally and seven (54%) by Cesarean section.

Four cases, one diagnosed with subdural hematoma and three with Grade I–II IVH, were delivered between 30 and 39 weeks (Cases 2, 9, 10 and 11), two by Cesarean section and two spontaneously, and had no neurodevelopmental deficiencies at 30–48 months' follow-up examination. Of the two fetuses with subdural hematoma, one pregnancy was terminated (Case 1) and the other (Case 2), which was diagnosed on routine sonography at 21 weeks, had complete resolution of the hematoma upon delivery and had no neurological sequelae at 40 months' follow-up (Figure 4). Two fetuses were cotwins of monozygotic pregnancies (Cases 6 and 10) and were delivered at 31 and 30 weeks, respectively. Of these two neonates, one had spontaneous regression of the IVH with no neurological

sequelae (Case 10) whereas the other, whose cotwin died *in utero*, was terminated following ultrasound diagnosis of Grade II lesion that was subsequently diagnosed as Grade III lesion by MRI and confirmed later as Grade IV by postmortem examination (Case 6).

One neonate with Grade III lesion (Case 16) was born at 37 weeks by Cesarean section and diagnosed by MRI to have aqueductal stenosis. Ventriculoperitoneal shunt was performed at 2 weeks, and follow-up neurological examination revealed moderate motor delay at 6 months. Of the eight cases with Grade IV lesion that opted to continue the pregnancy, four had spontaneous deliveries and four had Cesarean sections. One of the eight delivered fetuses (Case 31) had severe hypotony, germinal atresia and an abnormal electroencephalogram. The baby died in the pediatric intensive care unit at 2 months of

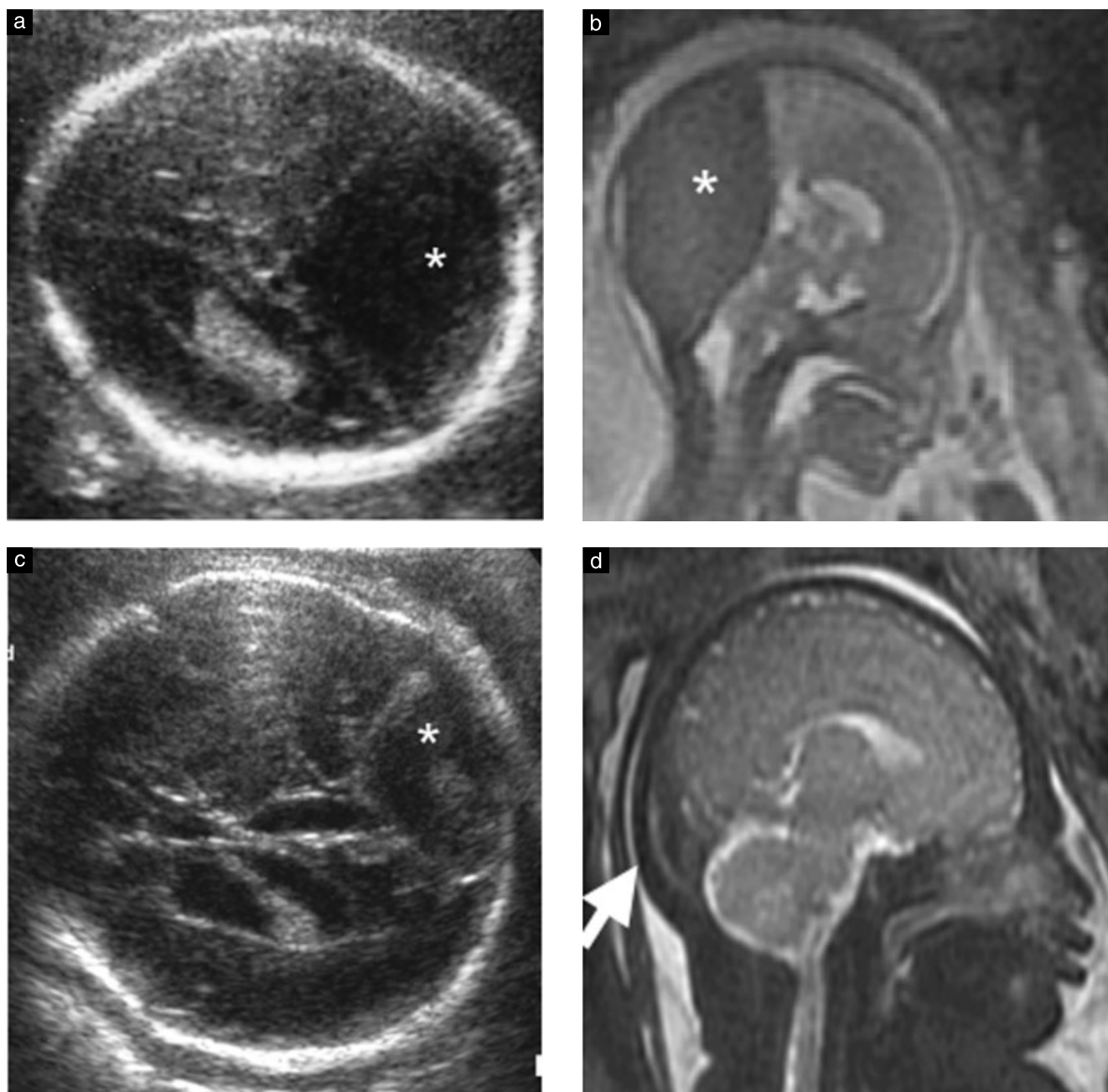


Figure 4 Huge fetal subdural supratentorial posterior hematoma diagnosed at 21 weeks (Case 2). (a) The asterisk is in the central portion of the hematoma. (b) Fetal magnetic resonance imaging (MRI) showing the hematoma (asterisk). (c) Ultrasound image showing partial resolution of the hematoma at 29 weeks (asterisk). (d) Fetal MRI showing complete resolution of the hematoma at 38 weeks (arrow).

age. The other seven cases had moderate to severe neurodevelopmental sequelae at 6–96 months' follow-up.

MRI studies

MRI was performed between 1 and 10 (mean $\pm$ SD, 2.8 ± 2.4) days following ultrasound diagnosis in 14/33 women: one following ultrasound diagnosis of subdural hematoma, in addition to four following ultrasound diagnosis of Grade II, three Grade III and six Grade IV IVH. It was found that MRI was more accurate in the prediction of additional findings in two cases of Grade II lesions and one of Grade III (21%). In all these cases, MRI studies indicated greater severity of lesions. In Case 5 the

diagnosis was changed from a unilateral lesion of 11 mm to a bilateral one of 14 mm; in Case 6 MRI diagnosed more extensive ventriculomegaly and the grading changed from Grade II to III; and in Case 15 MRI revealed both IVH as diagnosed by ultrasound, and intraparenchymal hemorrhage, changing the grading from III to IV.

DISCUSSION

In the present study we confirmed the neurodevelopmental status of most surviving fetuses, and related the sonographic and MRI extent of the fetal brain hemorrhage to their neurodevelopmental postnatal outcome. To our

knowledge, the present study is the largest series to focus on the outcome of antenatally diagnosed fetal ICH published in the English literature.

The incidence of perinatal stroke, defined as that which occurs between 28 weeks of gestation and 28 days of postnatal life, is reported to be 1 in 4000 live births^{3,4}. However, the incidences of fetal ICH and fetal stroke remain unknown, mainly because of deficiencies in diagnosis. Moreover, a number of patients might remain undiagnosed during the fetal and neonatal periods because the sequelae of ICH and fetal stroke may not present until later in the first year of postnatal life^{3,4}.

Observations of early cardiovascular hemodynamics suggest that the pathophysiology of IVH in human preterm infants may relate to a hypoperfusion–reperfusion cycle. About 80% of upper body blood flow goes to the brain, so when superior vena cava flow is very low, it is likely that the cerebral blood flow is also low. Data on humans have pointed to early low cerebral flow being a risk factor for IVH, and the germinal matrix is uniquely vulnerable to ischemic injury because of the watershed nature of the blood supply¹⁷. Lou recognized that an antecedent ischemic insult to the germinal matrix capillaries, possibly occurring antenatally, was probably important in the pathogenesis of IVH¹⁸.

While maternal and fetal risk factors for fetal stroke are suspected in some cases, including those of genetic, maternal, or placental etiology, in the majority of cases no identifiable risk factor is found^{3–6}. Maternal risk factors for fetal ICH include conditions such as platelet or coagulation disorders, seizures, trauma, viral or bacterial infection, febrile disease, amniocentesis, medications such as warfarin or cholestyramine and drugs such as cocaine^{2–6,19–21}. Fetal predisposing conditions include congenital coagulopathy with factor V and factor X deficiency, hemorrhage into a congenital tumor, twin–twin transfusion syndrome, demise of a cotwin, and fetomaternal hemorrhage^{22–24}. We found maternal or fetal medical conditions that might have alerted the physician to the possibility of fetal brain pathology only in 45% of cases.

There are limited data on neurodevelopmental prognosis when fetal ICHs are diagnosed antenatally^{12,14,25}. Ghi *et al.*¹⁴, in their extensive literature review of 93 cases and 16 cases of their own, reported a generally poor prognosis of newborns with antenatal ICHs, with about 40% of the fetuses dying either *in utero* or within the first month after birth, with fewer than half of the survivors neurodevelopmentally normal at short-term follow-up. Similar to our data, Ghi *et al.*'s experience with Grade I and II hemorrhages was limited; however, in both studies it was found that in lower grades complete disappearance of abnormal sonographic findings is associated with a better postnatal outcome. Conversely, in both studies it was found that intrauterine progression of the extent of the hemorrhage from a lower (Grade I–II) to a higher grade (which occurred in seven cases in the present study) is associated with a worse neurodevelopmental prognosis.

The present study has several limitations. One limitation of the study is the small number of liveborn fetuses with subdural hematoma and Grade I–II hemorrhage, but given the rarity of this entity only a very large study could gather enough low-grade cases to reliably conclude their prognosis. While it appears that Grade III–IV IVH is associated with poorer postnatal outcome than lower grade lesions, small sample size precludes comparison of Grade I–II vs. Grade III–IV as regards postnatal prognosis. Another limitation is that we did not send the placentae routinely for pathological examination in all cases. This might have clarified the etiology in some cases. The notable discrepancy between ultrasound and postmortem findings in some cases may result from autolysis or other changes observed during fixation of the brain tissue.

Associated anomalies might have an impact on outcome later in life. In the present study, however, survivors of all grades were without chromosomal anomalies or known genetic syndromes that might have influenced the outcome.

Fetal heart rate changes, such as sinusoidal pattern, might be the first indication of severe brain ischemia and damage^{26,27}, but only rarely will this finding be the presenting sign of fetal brain damage. In the present series only one case showed this pattern (Case 32). Another common finding in these cases is fetal anemia^{27,28}. In the present study, three cases developed intracranial lesions related probably to fetal anemia (two cases with death of monochorionic cotwin and a case with immune hydrops fetalis) as has recently been reported by others²⁹. With the advent of fetal middle cerebral artery peak systolic velocity measurements in the diagnosis of severe fetal anemia, it may be possible to detect and treat cases with severe fetal anemia, and potentially prevent fetal intracerebral hemorrhage in these cases^{30,31}.

The present case series showed a higher incidence of left hemisphere IVHs than right-sided hemorrhages, as has been described in other series of perinatal ischemic injuries^{3,6,32}. The greater frequency of left-side hemispheric hemorrhage may be related to an inherent susceptibility of the blood vessels in the left hemisphere or to a better right vs. left carotid blood supply in fetal hypotensive situations^{3,6}.

The role of MRI in the evaluation of fetal cerebral hemorrhagic or ischemic lesions is controversial³³. MRI is usually performed as an additional measure to clarify ventricular and parenchymal involvement. Our limited data do not allow definitive conclusions on the importance of MRI in the evaluation of IVH grading to be drawn. However, it seems that in considering whether to perform MRI, in several cases of prenatal diagnosis of intracranial hemorrhagic insult MRI was more accurate than ultrasound, and whenever grading differed between the two modalities it was more severe following MRI. While it cannot be ruled out that *in-utero* progression of some lesions occurred between the ultrasound and MRI examinations being performed, the tangible possibility

of greater precision of MRI must be considered. Larger studies are needed to investigate this issue.

In conclusion, fetal stroke represented as parenchymal insult or IVH of Grade III and IV carries a high risk of postnatal neurodevelopmental deficiencies. MRI appears to contribute to the accuracy of diagnosis, particularly in Grade II and III intraventricular insults. Unilateral left-sided lesions are much more common than right-sided ones.

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